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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/045,292	10/18/2001	Lieven Stuyver	09797.0004-00	4833

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EXAMINER	
MCINTOSH III, TRAVISS C	
ART UNIT	PAPER NUMBER
1623	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/045,292	STUYVER ET AL.	
	Examiner	Art Unit	
	Traviss C. McIntosh	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-58* is/are pending in the application.

4a) Of the above claim(s) *6-34,37,38,43,45-49,52,53 and 58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,35,36,39-42,44,50,51 and 54-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/21/02 & 10/31/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I in the reply filed on 10/19/2006 is acknowledged. The traversal is on the ground(s) that there is considerable overlap between the restricted groups, all of which share a common core. This is not found persuasive. It is noted that the claims pending contain a vast number of divergent compounds, many of which only share a few carbon atoms as their "common core". Applicants also argued that at the very least the application be restricted as set forth on pages 11-12. The examiner does agree in part with applicants arguments, and upon a review of the art, the examiner sets forth the following groups as being restricted.

1) Original Groups I-VI, LXVII, and LXIX-LXXI, claims 1-5, 35-36, 39-42, 44, 50-51, and 54-57 are now combined as new Group I.

2) Original Groups VII-XV, claims 6-9, and 44, are now combined as new Group II.

3) Original Groups XVI-XXXIII, claims 10, 11, and 44, are now combined as new Group III.

4) Original Groups XXXIV-XXXVII, claims 13-16, and 44, are now combined as new Group IV.

5) Original Groups XXXVIII-XXXIX, claims 17, 18, and 44, are now combined as new Group V.

6) Original Groups XL-XLV, claims 19-21 and 44, are now combined as new Group VI.

7) Original Groups XLVI-LI, claims 22-26 and 44, are now combined as new Group VII.

8) Original Groups LII-LIX, claims 27-28 and 44, are now combined as new Group VIII.

9) Original Groups LX-LXIII, claims 29 and 44, are now combined as new Group IX.

10) Original Groups LXIV-LXVI, claims 30-34 and 47-49, are now combined as new Group X.

11) Original Group LXVII, claims 37, 38, 43, 52, 53, and 58, is now new Group XI.

It is noted that applicants also argued that original groups LXIV-LXVII, LXIX, and LXXI should be rejoined with Group I, as they are species of the compounds of Group I, however, the examiner notes that these compounds are outside the scope of those as claimed in claim 1, as the later claims, claim 30 for example, comprise a moiety in the 2'-position (P^2) which is not in the compounds of claim 1, wherein P^2 is outside the scope of the compounds as set forth in claim 1. As such, these are not seen to be species of the compounds of claim 1, and applicant's arguments are not convincing.

Claims 6-34, 37-38, 43, 45-49, 52-53, and 58 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

An action on the merits of claims 1-5, 35-36, 39-42, 44, 50-51, and 54-57 is contained herein below.

Claim Objections

Claim 1 is objected to because of the following informalities: it appears that the claim contains multiple periods, such as at the end of line 2 on page 203, and at the end of line 5 on page 203. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 35-36, 39-42, 44, 50-51, and 54-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of *Flaviviridae, Orthomyxoviridae,* or *Paramyxoviridae* viral infections, or treating abnormal cellular proliferation, does not reasonably provide enablement for prevention of the same. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in ***In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)***. A conclusion of lack of enablement means that, based on the evidence regarding a fair evaluation of an appropriate combination of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

These factors include:

(A) The breadth of the claims;

(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims - The nature of the invention

The claims are drawn to a method of treating or preventing *Flaviviridae, Orthomyxoviridae,* or *Paramyxoviridae* viral infections, or treating or preventing abnormal cellular proliferation, using the various claimed nucleosides. It is noted that abnormal cellular proliferation reads on cancer, as such, applicant's claims encompass methods of preventing cancer, of all types.

The state of the prior art

There are various known nucleoside derivatives which have efficacy in treating viral infections, as seen by Devos et al. (US 2004/0110718). Various compounds are known to have efficacy in cancer therapy, such as 4,6-O-benzylidene-D-glucopyranose and benzaldehyde for example, as seen in Kochi et al. (US Patent 4,778,785) and Katayama et al. (US Patent 4,613,588). At present, there are no known agents capable of preventing all types of cancer or all *Flaviviridae, Orthomyxoviridae,* or *Paramyxoviridae* viral infections.

The level of predictability in the art

The examiner acknowledges the probability and predictability that the active agent has efficacy in treating certain conditions associated with cancer, and treating the claimed viral

diseases, however the art is silent with regard to the predictability of effectively preventing the development of cancer or the viral infections by administering the claimed compounds.

The amount of direction provided by the inventor

The instant specification is not seen to provide adequate guidance which would allow the skilled artisan to extrapolate from the disclosure and examples provided to use the claimed method commensurate in the scope with the instant claims. There is a lack of data and examples which adequately represent the scope of claim as written, i.e., nothing showing any preventative therapy. The examiner notes, there has not been provided sufficient instruction or sufficient methodological procedures to support the alleged efficacy instantly asserted.

The existence of working examples

The working examples set forth in the instant specification are directed to the use of various compositions in testing their antiviral activity or ability to inhibit cell proliferation of various cell lines. There has not been provided sufficient evidence which would warrant the skilled artisan in virology or oncology, to accept the data and information provided in the working examples as correlative proof that a healthy individual would never become afflicted with any of the viral conditions or any cancerous condition if subjected to the instantly claimed therapy.

The quantity of experimentation needed to make and use the invention based on the content of the disclosure

Indeed, in view of the information set forth supra, the instant disclosure is not seen to be sufficient to enable the use of any of the compositions to prevent the development of the claimed

viral diseases or cancer without undue experimentation. One skilled in the art could not use the entire scope of the claimed invention without undue experimentation.

Reasonable guidance with respect to preventing any condition relies on quantitative analysis from defined populations which have been successfully pre-screened and are predisposed to particular types of the condition. This type of data might be derived from widespread genetic analysis, cancer clusters, or family histories. The essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in advance of the clinical condition and *link* those results with subsequent histological confirmation of the presence or absence of disease. This irrefutable link between antecedent drug treatment and subsequent knowledge of the prevention of the disease is the essence of verification of a valid preventive agent.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 35-36, 39-42, 44, 50-51, and 54-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite wherein the claim is drawn to a method comprising administering an effective amount of a compound of formula (I) or (II), however, the claim then defines formulas [I-a], [I-b], [I-c], [II-a], [II-b], and [II-c]. It is noted that formulas I-a, I-b, etc., are not seen to be the same as formulas I or II. Changing the claim to read that compounds I-a, I-b, I-c, II-a, II-b, or II-c are administered, not formulas I or II, would overcome the instant rejection.

Claims 1, 35-36, 39-42, 44, 50-51, and 54-57 are indefinite wherein the claims fail to state to whom the compound is administered. Changing the claims to state "to a patient in need thereof" would be seen to overcome the instant rejection.

Claim 1 is indefinite wherein the claim defines various variables, such as X^1 and X^2 for example, as optionally being "halogen (F, Cl, Br, or I)". The use of the parenthetical phrase leaves uncertainty as to whether applicants intend the moiety to be any halogen, or just F, Cl, Br, or I. Correction is required in all occurrences.

Claim 1 language used in defining "R^2 and $R^{2'}$" and "R^3 and $R^{3'}$" is indefinite. Applicants have not used proper Markush language, i.e.,, "selected from the group consisting of X, Y, **and** Z", or "is X, Y, **or** Z". Changing the claim to read "each R^2 and $R^{2'}$ is independently hydrogen, halogen, OH, ..., or CO_2H" would overcome the instant rejection.

Claim 1 is indefinite wherein the claim provides that each R^4, $R^{4'}$, etc., is independently arylalkyl "such as unsubstituted or substituted phenyl or benzyl". It is unclear if applicants intend these to be arylalkyl groups, or only the phenyl or benzyl groups.

Claim 2 recites the limitation that R^1 and $R^{1'}$ are D, or R^2 or R^3 are O-Ms in the table. There is insufficient antecedent basis for these limitations in the claim. The compound of claim 1 does not afford for these variables at these positions. Due to the size of the tables, applicants are encouraged to ensure they have support in the claims from which they depend all of the variables as set forth in the tables.

Claim 3 recites the limitation that $R^{3'}$ is O-Ac in the table. There is insufficient antecedent basis for this limitation in the claim as the claim from which it depends does not afford for $R^{3'}$ to be O-Ac.

Claims 4 and 5 are indefinite wherein the claims provide that various compounds have F in the R^2 position, however, it is noted that according to claim 1, that "at least one of R^2 and $R^{2'}$ is H", and since claims 4 and 5 are drawn to compounds only comprising the moiety R^2, that this cannot be F. Correction is required.

Claims 1-5, 35-36, 39-42, 44, 50-51, and 54-57 are drawn to methods for the "treatment or prophylaxis of a host exhibiting a viral infection or abnormal cellular proliferation". It is noted that it is unclear if the hosts actually have the claimed diseases, or just exhibit them. It is noted if one were to exhibit a viral infection, it would appear that only the symptoms are being seen, and thus, since the same symptoms are produced by many divergent causes, it is unclear if the host must actually have the claimed disorders. It is noted that the examiner is interpreting these to read as methods for the treatment or prophylaxis of a host having a ...viral infection. Moreover, clarity is respectfully requested regarding how one could prevent a disorder that the host already has. That is, if the host is already exhibiting the disorder, or already has the disorder, how can one then prevent the same?

Claims 35-36 are indefinite wherein the claims state "its β-L enantiomer", as the compound as set forth is already in its β-L form. It is noted that the examiner believes applicants intended this to read or "its β-D enantiomer", as this would be the alternative enantiomer in relation to the compound depicted.

Claims 35-36, and 50-51 are indefinite wherein the claims state that various variables are "the same as defined previously". However, as defined previously where? In the instant specification, in a different patent, in a foreign non-patent document? Applicants should include in independent claims all of which is required in the claim, and not point elsewhere in the claim.

Claim 42 is indefinite wherein the claim is drawn to a method using a compound of the general formula I or II, but then lists a specific formula for a species, and does not define formulas I or II. Removing the phrase "(I) or (II)" would overcome the instant rejection.

Claim 44 is indefinite wherein the claim depends from withdrawn claims. Correction is required.

Claims 50 and 51 are indefinite wherein the claims are drawn to using a β-D nucleoside of formula XXII or as set forth in claim 51. However, it is noted that the compounds depicted as formula XXII and as in claim 51 are in their β-L form, not the β-D form as set forth. Applicants also state the compound can be in "its β-L enantiomer" also, however, as set forth supra, the compound is depicted in its β-L form already. Correction is required.

All claims which depend from an indefinite claim are also indefinite. ***Ex parte Cordova, 10 U.S.P.Q. 2d 1949, 1952 (P.T.O. Bd. App. 1989).***

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-5, 35, 44, and 50 are rejected under 35 U.S.C. 102(b) as being anticipated by Filippini et al. ("Can HCV affect the efficacy of anti-HIV treatment?, Archives of Virology, 145(5), 937-944, May 2000).

It is noted that the examiner does not believe the provisional application 60/241,488, filed 10/18/2000, to completely support the instantly pending claims, as such, the instant claims only obtain the priority date of the provisional application 60/282,156 filed 4/6/2001. Moreover, it is noted that while claims 2-5 limit the compounds used in the method of claim 1, claims 2-5 do not require the compounds limited therein to actually be administered.

Filippini et al. disclose a method of treating patients with HCV compositions comprising Zalcitabine (see 938, "Antiretroviral treatment"), which is known to be 2'-3'-dideoxycytidine, which is a species of the claims rejected above, specifically the compounds of claims 35 and 50 wherein P^1, R^1, and D are all H. Filippini et al. inherently disclose the methods as claimed, as they administer the same compound (Zalcitabine) to the same population, patients with HCV, and thus must have produced the same results.

Claims 1-5, 35-36, 39-42, 44, 50-51, and 54-57 are rejected under 35 U.S.C. 102(e) as being anticipated by Devos et al. (US 2004/0110718).

Devos et al. disclose methods of treating HCV by administering compounds overlapping in scope with those claimed in the instant application (see [0008]-[0126], also see compounds 239-241, which are the same as the species claimed in claims 40 and 55 of the instant application). Devos note that HCV belongs to the family of Flaviviridae (see [0006]). Devos teaches the compounds can be 2'-3'-dideoxy (where R^1, R^2, and R^3 are all H) and the base can be

F-substituted (R13 can be halogen, see also compound 234 which uses F in this location) as in claims 35, 36, 50, and 51 of the instant application. Devos teach that the compounds can be 3'-deoxy (where R^1 and R^3 are H and R^2 is OH) as in claims 39 and 54 of the instant application. Devos teaches that halogen can be in the 6-position as in claims 42 and 57 of the instant application where R^5 is halogen.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Traviss C. McIntosh whose telephone number is 571-272-0657. The examiner can normally be reached on M-F 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Traviss McIntosh
December 27, 2006

Shaojia A. Jiang
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1/3/07